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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| EXAMINER | |
|---|---|
| MARVICH, MARIA | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1633 | |

DATE MAILED: 07/10/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/607,752 | DELCAYRE, ALAIN | |
| | Examiner | Art Unit | |
| | Maria B. Marvich, PhD | 1633 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *18 August 2005*.

2a)☒ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *3-8,11 and 13-28* is/are pending in the application.

4a) Of the above claim(s) *6-8,11,13 and 16-23* is/are withdrawn from consideration.

5)☒ Claim(s) *14,15,24 and 28* is/are allowed.

6)☒ Claim(s) *17-23 and 25-27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☒ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

This office action is in response to a response to an amendment filed 1/18/06 and 4/5/06. Claims 1-5, 9, 10 and 12 have been cancelled. Claim 28 has been amended. Claims 29-31 have been added. Claims 6-8, 11 and 13-28 are pending in this application.

The terminal disclaimer filed on 1/18/06 disclaiming the terminal portion of any patent granted on this application, which would extend beyond the expiration date of US patent No. 6,346,898 has been reviewed and is accepted. The terminal disclaimer has been recorded.

### *Response to Amendment*

Any rejection of record in the previous action not addressed in this office action is withdrawn. The new grounds of rejection herein were necessitated by amendment and, therefore, this action is final.

Newly submitted claims 29-31 are directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: Claims 29-31 are drawn to inventions of Groups III and IV as set forth in the restriction requirement mailed 11/4/05, which was not elected. Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 29-31 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

Claims 17-23 are drawn to subject matter that has been found allowable and therefore are rejoined. Therefore, claims 6-8, 11, 13, 16 and 29-31 have been withdrawn and claims 14, 15 and 17-28 are under examination in this application.

### *Claim Rejections - 35 USC § 112*

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claims 17-21 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. **These are new rejections necessitated by applicants' amendment.**

Claim 17 is vague and indefinite in that the metes and bounds of "enhancing an immune response" are unclear. The claim recites that an immune response is enhanced by administration of the composition. However, there is not step recited in which an immune response is induced that is enhanced. Given the lack of steps for an initial immune response, it is unclear how the immune response can be "enhanced".

Claim 21 is vague and indefinite in that the metes and bounds of "induce lone-term memory cells" are unclear. It is unclear what about the long-term memory cells are being induced. Grammatically, the sentence appears to be incomplete.

### *Claim Rejections - 35 USC § 112, first paragraph*

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 25-27 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not

described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **This rejection is maintained for reasons of record in the office action mailed 11/4/05 and restated below.**

Applicants claim a fusion protein comprising a sequence having 95% identity to SEQ ID NO: 116, which possesses the ability to stimulate proliferation or interferon-gamma (IFN-γ) secretion in T cells from individuals that have been exposed to *M. tuberculosis*.

The written description requirement for genus claims may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant identifying characteristics, i.e. structure or other physical and/or chemical properties, by functional characteristics coupled with known or disclosed correlations between function and structure, or by a combination of such characteristics sufficient to show that the applicant was in possession of the claimed genus.

Applicants recite a genus of fusion proteins that are related by having at least 95% identity to SEQ ID NO: 116. Applicants have not demonstrated the structural requirements of SEQ ID NO: 116 such that a person of skill in the art would know which amino acids are absolutely required for function and which can be altered to within 95% identity to SEQ ID NO: 116. Functionally, any fusion peptides that vary from SEQ ID NO: 116 must possesses the ability to stimulate proliferation or interferon-gamma (IFN-γ) secretion in T cells from individuals that have been exposed to *M. tuberculosis*. However, applicants have only reduced to practice the instant invention with a recombinant multi-epitope that is SEQ ID NO: 116 as well as the individual epitopes used to generate SEQ ID NO: 116, which they demonstrate

stimulate proliferation of cells and secretion of IFN-γ from the cells. Specifically, applicants have identified eight plasmids encoding immunogenic -epitopes from *Mycobacterium vaccae*, which have been demonstrated to stimulate proliferation of T-cells and IFN-γ secretion. *Mycobacterium vaccae* is non-pathogenic to humans and therefore, applicants propose use of epitopes from this organism to enhance immune response as well as to treat infectious disorders such as tuberculosis and other mycobacterial infections in humans and domestic mammals or livestock and to treat immune system disorders. Cloned *M. vaccae* fragments were inserted into pcDNA3 vectors comprising an hGH PCR fragment (pCDNA3-hGH), which encodes the hGH signal peptide and a concatenating linker used to connect the signal peptide to the epitope. The signal peptide was used to facilitate protein secretion. Expression of these recombinant epitopes in peripheral blood mononuclear cells *in vitro* lead to proliferation of the cells and IFN-γ production from the cells (table 2 and 3). Expression in mice *in vivo* induced a reduction of CFUs.

The eight cloned epitopes were then used to generate three multi-epitope constructs assembled into single constructs in pcDNA3-hGH vectors and in pET16 vectors and are disclosed as SEQ ID NO:s 79-81and 116 (example 4). SEQ ID NO:81 or ME/D, consists of each one of the 8 epitopes described above in a particular order. The insert of ME/D in pCDNA3-hGH was subcloned into pET16. It is not disclosed but presumed that this vector lacks the signal sequence and concatenating linker of ME/D and hence would correspond to SEQ ID NO:116 as it is described as the amino acid sequence of the ME/D fusion polypeptide minus the signal peptide and concatenating linker. In example 5, the multi-epitope constructs were used to immunize mice. Example 5 teaches that ME/D was injected intraperitoneally with recombinant

ME/D (rME/D). Three weeks later, mice were challenged with *M. tuberculosis*. CFU formation in the lung and spleen was demonstrated suggesting immunization. Example 6 demonstrates subcutaneous, intraperitoneal or intramuscular injection of the recombinant fusion protein into the footpads of mice lead to lymph node and spleen cell proliferation as well as secretion of IFN-γ. In this example, rME/D stimulated memory T cells from mice infected with M Tuberculosis to produce large amounts of IFN–γ. PBMC cells comprising these vectors were stimulated to proliferate and secrete IFN-γ. In example 8, cynomolgus monkeys were immunized with rME/D leading to proliferation of lymphocytes. It is not completely clear whether SEQ ID NO:81 or SEQ ID NO:116 is used in these experiments as the constructs used in the examples is generically referred to as ME/D. Only in example 7 is it disclosed specifically that the epitopes contained within ME/D were expressed using pET16.

An adequate written description of the invention defined by the claims requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it; what is required is the knowledge in the prior art and/or a description as to the availability of a representative number of species of claimed nucleic acid sequences. Recombinant technology for the generation of fragments or for detecting related sequences is highly developed. However, the ability to determine *a priori* whether a fragment or related sequence can function in the recited invention is not. A particular protein sequence determines the protein's structural, and functional properties, and a predictability of a representative number of claimed polypeptide sequences that display noteworthy biological properties requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e., expectedly intolerant to modification), and detailed knowledge of

the ways in which a protein's structure relates to its functional usefulness (see Tertiary structure, Protein structure prediction and Smith et al). Bowie et al (applicant provided) teach that it is essential to know the residues involved in function. For example replacing the Asp in the catalytic triad of trypsin with Asn results in a 10(4) reduction in activity (see e.g. page 1306, vol 2, paragraph 3). Therefore, the ability to predict *a priori* which sequences that will meet a particular goal is poorly developed. In addition, by claiming any fusion protein with 95% identity to SEQ ID NO: 116 that achieve a result without defining what means will do so is not in compliance with the written description requirement. Rather, it is an attempt to preempt the future before it has arrived. (See Fiers 7. Reveb 25 USPQZd 1601 (CA FC 1993) and Regents of the Univ. Calif v. Eli Lilly & Co. 43 USPQZd 1398 (CA FC, 1997)). In the instant case, applicants have not demonstrated that variance of or deletion of any, some or all of the amino acids of the fusion peptides would result in a protein that can function similarly. Therefore, the relationship between structure and function is unclear as neither applicant nor the prior art provide structural requirements of the SEQ ID NO:116 that are able to stimulate proliferation of T-cells and IFN-γ secretion. Furthermore, applicants have only demonstrated that they are in possession of ME/D disclosed as SEQ ID NO:116. Ultimately this is a single species of polypeptides. Given the large size and diverse nature of the recited proteins and the inability to determine which will also possess the ability to stimulate proliferation of T-cells and IFN-γ secretion, it is concluded that the invention must be empirically determined. In an unpredictable art, the disclosure of a single species would not represent to the skilled artisan a representative number of species sufficient to show applicants were in possession of the claimed genus.

***Response to Arguments***

Applicants argue that there is no basis for a *per se* rule requiring disclosure of complete DNA sequences or limiting DNA claims to only the sequence disclosed. In the instant case, applicants argue that the recited fusion proteins possess sufficient common identifying characteristics to SEQ ID NO:116 such as specific percentages of sequence identity and clearly recited functional characteristics to clearly distinguish the claimed fusion proteins from other materials.

Applicants' arguments filed 2/4/05 have been fully considered but they are not persuasive. Applicants have recited a broad genus of fusion proteins encoded with at least 95% sequence identity to a polypeptide having an amino acid sequence of SEQ ID NO: 116. Applicants have not provided the structural requirements of SEQ ID NO:116 by simply disclosing the sequence and stating that polypeptides that are encoded by sequence with 95% similarity to SEQ ID NO:116 are a part of the invention. A number of fusion proteins fit into this broad genus but the skilled artisan cannot envision the detailed structure of the broad class of proteins given the lack of adequate written description. Applicants' disclosure has amounted to a statement that the protein is part of the invention and a reference to a potential method for isolating it, by sequence identity. Disclosure of the sequence of SEQ ID NO:116 is not accompanied by structural requirements of SEQ ID NO:116 such that members of the genus can be identified.

***Claim Rejections - 35 USC § 112, first paragraph***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 17-23 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for inducing Th1 cytokine responses and anti-epitope antibodies and T-cell proliferation, does not reasonably provide enablement for enhancing any immune response or treating any immune disorder or infectious disease. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. **This is a new rejection necessitated by applicants' amendment.**

The test of enablement is whether one skilled in the art could make and use the claimed invention from the disclosures in the patent coupled with information known in the art without undue experimentation (*United States v. Telectronics, Inc.*, 8 USPQ2d 1217 (Fed. Cir. 1988)). Whether undue experimentation is required is not based on a single factor but is rather a conclusion reached by weighing many factors (See *Ex parte Forman*, 230 USPQ 546 (Bd. Pat. App. & Inter, 1986) and In *re Wands*, 8USPQ2d 1400 (Fed. Cir. 1988); these factors include the following:

**1) Nature of invention**. Instant claims 17-23 are drawn to a method of enhancing an immune response in a patient as well as treatment of a disorder selected from the group consisting of immune disorders and infectious disorders comprising administration of a composition comprising SEQ ID NO:116.

**2) Scope of the invention**. SEQ ID NO: 116 is a polypeptide constructed from multiple epitopes isolated from *M. vaccae.* The fusion protein possesses the ability to stimulate proliferation or interferon-gamma (IFN-γ) secretion in T cells from individuals that have been exposed to *M. tuberculosis*. The claims recite use of the fusion protein to enhance any immune response as well as treat any immune disorder or any infectious disorder simply by administration of the protein.

**3) Number of working examples and guidance**. The specification teaches that tuberculosis is caused by infection with *Mycobacterium tuberculosis*. Applicants propose that *Mycobacterium vaccae* a related but non-pathogenic relative be used to stimulate an immune response as well as to prevent and treat infectious and immune disorders. Applicants propose that the *M* vaccae epitope of the instant invention will activate T cells and NK cells, stimulate production of cytokines in human PMBC and produce anti-epitope antibodies, induce long-term memory cells and/or enhance an immune response against an antigen.

The specification teaches isolated of eight epitopes that were then used to generate three multi-epitope constructs including SEQ ID NO:116. In example 5, the multi-epitope constructs were used to immunize mice. Example 5 teaches that ME/D was injected intraperitoneally with recombinant ME/D (rME/D). Three weeks later, mice were challenged with *M. tuberculosis*. CFU formation in the lung and spleen was demonstrated suggesting immunization. Example 6 demonstrates subcutaneous, intraperitoneal or intramuscular injection of the recombinant fusion protein into the footpads of mice lead to lymph node and spleen cell proliferation as well as secretion of IFN-γ. In this example, rME/D stimulated memory T cells from mice infected with M Tuberculosis to produce large amounts of IFN–γ. PBMC cells comprising these vectors were

stimulated to proliferate and secrete IFN-γ. In example 8, cynomolgus monkeys were immunized with rME/D leading to proliferation of lymphocytes. It is not completely clear whether SEQ ID NO:81 or SEQ ID NO:116 is used in these experiments as the constructs used in the examples is generically referred to as ME/D. Only in example 7 is it disclosed specifically that the epitopes contained within ME/D were expressed using pET16.

**4) State of the art**. *Mycobacterium vaccae* has been proposed in treatment of allergic disorders as well as tuberculosis and cancer. In none of these efforts has treatment of a single disorder been demonstrated. In fact a recent review of the art has demonstrated no benefit from immunotherapy with *vaccae* (see Garner et al) or ability to treat asthma (see e.g. Shirtcliffe et al). Therefore, the art of treatment of known disorders or disease with *vaccae* is unpredictable. Furthermore, while applicant propose treatment of any disorder or disease by use of the epitope from M *vaccae,* Qazi et al teach the role of vaccae as an adjuvant for induction of immune response during infection is due heat shock proteins from whole-cell preparations are responsible for this induction(see e.g. page 7691, col 2, ¶ 2). This response would not be expected in the absence of the whole cell extract. As well, the art has demonstrated down-regulation of Th2 activity. Therefore inductive response to vaccae is limited to Th1 response.

**5) Unpredictability of the art**. Applicants propose multiple broad and divergent responses that are induced by administration of SEQ ID NO: 116. However, applicants do not demonstrate or disclose enhancement of any immune response or treatment of any infectious disease or any immune disorders. The art of immune responses as well as infectious disorders encompasses a widely divergent and broad art. The art of treating any number of disorders that are immune or infectious by nature by administration of SEQ ID NO:116 is highly unpredictable

given the divergent and unknown nature of the recited disorders. Similarly, enhancement of any immune response by administration of SEQ ID NO:116 is highly unpredictable given the unknown nature of the immune response to be enhanced.

**6) Amount of Experimentation Required.** The invention recites use of a SEQ ID NO;116 to treat or enhance a broad group of immune response or disorders as well as broad range of infectious disorders. In view of the unpredictability of the art of predicting the immune response or immune disorder or infectious disorder that could be enhanced and/or treated by SEQ ID NO: 116: undue experimentation would be required to practice the claimed methods with reasonable expectation of success, absent a specific and detailed description in the specification.

***Conclusion***

Claims 17-23 and 25-27 are rejected.

Claims 14, 15, 24 and 28 are allowable.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37

CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maria B. Marvich, PhD whose telephone number is (571)-272-0774. The examiner can normally be reached on M-F (6:30-3:00).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, David Nguyen, PhD can be reached on (571)-272-0731. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Maria B Marvich, PhD
Examiner
Art Unit 1633

DAVE TRONG NGUYEN
SUPERVISORY PATENT EXAMINER